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Original Article

Physical Activity and the incidence of sepsis: A 10-year observational study among 4 million adults

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Abstract *Background:* As the group at high risk for sepsis is increasing with the aging of the population, physical activity (PA), which has beneficial effects on various diseases, needs to be considered as a personalized prevention strategy for sepsis without direct anti-sepsis drug.
Purpose: To examine the association between the amount of PA (based on intensity, duration, and frequency) and the incidence rates of sepsis and mortality after sepsis.
Methods: This was a large-scale, retrospective, longitudinal cohort study using data from the Korean National Health Insurance Service and the biennial general health screening program. The amount of PA self-reported at the time of the health screening was categorized as non-PA, mild (<500 metabolic equivalents [METs]-Min/Week), moderate (500—1000), severe (1000—1500), and extreme (≥1500). The multivariable regression model was adjusted for age, sex, income, body mass index, smoking, alcohol consumption, diabetes, hypertension, dyslipidemia, and chronic diseases.
Results: From 4,234,415 individuals who underwent a health screening in 2009, 3,929,165 subjects were selected after exclusion for wash-out period and a 1-year lag period, and then observed for the event of sepsis or all-cause death until December 2020. During a median 10.3 years of follow-up, 83,011 incidents of sepsis were detected. The moderate-PA group

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showed the lowest incidence (1.56/1000 person-years) and risk for sepsis, with an adjusted hazard ratio (aHR) of 0.73 (95% CI, 0.72—0.75, $P < 0.001$) compared with the non-PA group. The occurrence of sepsis among people aged ≥65 years and ex-smokers were significantly lower in the moderate-PA group (aHR; 0.77, 95% CI; 0.74—0.79; and 0.68, 0.64—0.71, respectively, $Ps < 0.001$). The long-term all-cause mortality after sepsis was significantly lower in the PA group than in the non-PA group (overall $P = 0.003$).

Conclusions: Physical activity is associated with a lower risk of sepsis, especially in elderly people who have the highest incidence of sepsis. The protective effects of aerobic PA on sepsis might need to be incorporated with other interventions in sepsis guidelines through the accumulation of future studies.

Introduction

Sepsis is a dysregulated inflammatory condition that deviates from homeostatic immune responses against the growth of pathogens and can result in multi-organ dysfunction (MOD) caused by tissue hypoperfusion, with lethal outcomes.[1—3] The Global Burden of Disease (GBD) study estimated that 48.9 million adults are diagnosed with sepsis each year, and sepsis-related mortality comprised about one-fifth of all global deaths in 2017.[4] Although the incidence and fatality of sepsis have been declining since 1990,[4] the periodic GBD dataset reveals that the global burden of sepsis remains unacceptably large.[4,5] Moreover, deep understanding of its complex pathophysiology and clinical trials of bundle approaches intended to achieve precise targets in the early stage have failed to dramatically improve the short- or long-term prognosis of sepsis.[6—11] In-hospital mortality for critically ill sepsis patients receiving treatment in an intensive care unit and those with hospital-acquired sepsis still approaches 50%.[12,13] Together with recent large-scale epidemiologic findings and the limitations of new innovative treatment modalities, an increase in the number of individuals at high risk for sepsis due to aging and the use of immunosuppressive drugs elevates the need for individualized sepsis preventive strategies that incorporate lifestyle modification.[14,15]

Aerobic exercise, such as walking, running, and bicycling, has long been considered a valuable physical activity (PA) for health promotion and the prevention of chronic illnesses such as hypertension, cardiovascular diseases, cancer, diabetes mellitus (DM), and cognitive dysfunction.[16—21] Recently, the physiological benefits of PA have been demonstrated in sepsis animal models. A moderate intensity of PA reduced pro-inflammatory cytokines and chemokines, including tumor necrosis factor-α, interleukin (IL)-1β, C-X-C motif chemokine ligand (CXCL)-1, and CXCL-8, and increased anti-inflammatory cytokines such as IL-1 receptor antagonist protein and IL-10, and those changes offered protection against MOD and death immediately following the induction of sepsis.[22,23]

Even though several *in vivo* experiments have shown that PA could ameliorate the exaggerated inflammatory response induced by sepsis, reports about the association between PA and sepsis in humans have been scant. Considering the various advantages of PA on health, this large-scale, long-term study aimed to demonstrate a correlation between PA and the incidence of sepsis and short- and long-term mortality after sepsis.

Methods

Study oversight and subject selection

We performed this retrospective longitudinal cohort study using the Korean National Health Insurance Service (KNHIS) system. KNHIS provides a free voluntary biennial National Health Screening (HEALS) program for adults older than 20 years.[24—26] The standardized KNHIS-HEALS examinations for public health promotion include anthropometric measurements, blood pressure (BP), laboratory tests for fasting glucose and chemistry, and self-report questionnaires about comorbidities, alcohol consumption, smoking, and patterns of PA (Table S1).[26] Our last 7-day recall survey for PA has been evaluated to be adequate for assessing each subject's level of PA in the national monitoring.[27,28]

From the KNHIS-HEALS database,[26] we selected 4,234,415 individuals who underwent a HEALS examination between January 2009 and December 2009 as feasible subjects. The baseline date for each subject was the day on which the HEALS exam was performed. To clarify the potential interaction by minimizing the influence of confounding variables and removing censored data, we applied a wash-out period between January 2002 and the baseline date, along with a 1-year lag period after cohort entry.[29] We excluded 7932 subjects who had been diagnosed with sepsis during the wash-out period of ≥7 years before cohort entry and 285,822 subjects with missing HEALS data. After further removal of 11,496 subjects whose follow-up was terminated early due to sepsis or death during the lag period, a total of 3,929,165 individuals were included in the final cohort (Fig. 1).

We joined the KNHIS-HEALS database with the KNHIS-National Health Information database using anonymous identification numbers for the cohort subjects to identify whether events occurred during the observation period. The primary and secondary events were a diagnosis of

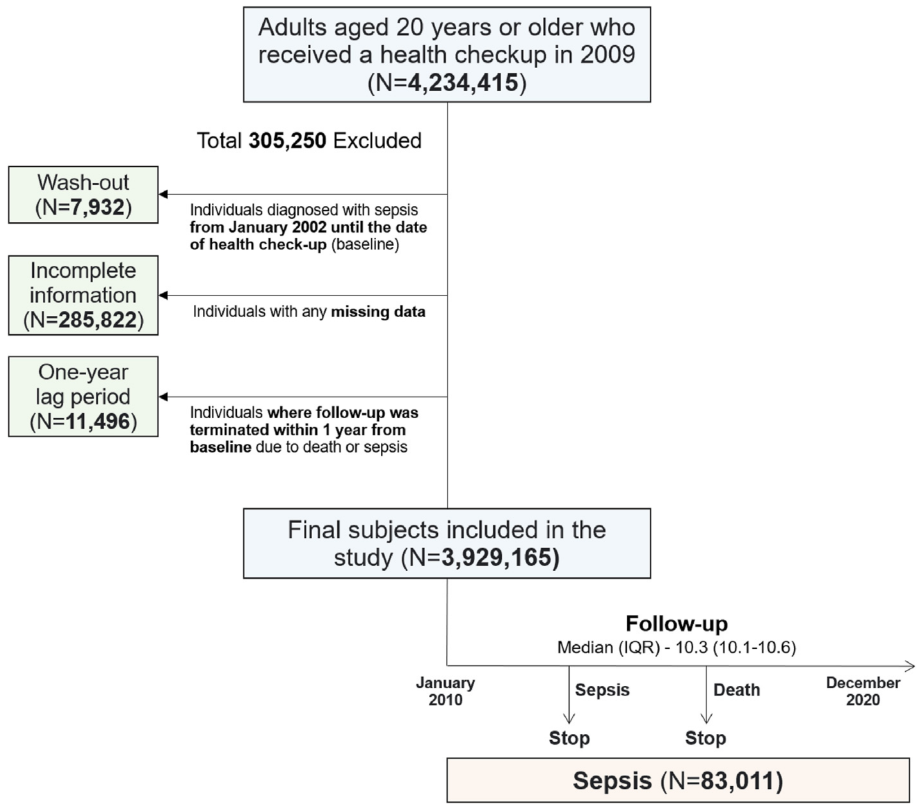

Figure 1. Schematic flow chart for the process of study subject selection and follow-up design. Abbreviations. IQR, interquartile range.

sepsis and all-cause death within 30 days or during the observation period after sepsis, respectively. Follow-up was stopped when the first diagnosis of sepsis or death occurred, and if neither of those happened, the end date of measurement was December 31, 2020.

Categorization of physical activity amount

For the self-assessment of PA, three questions were modified from the International Physical Activity Questionnaire Short Form of the World Health Organization (WHO), which has verified reliability: how many days per week do you engage in light-intensity (≥30 min/d), moderate-intensity (≥30 min/d), and vigorous-intensity (≥20 min/d) activity?[26,27,30] We used metabolic equivalents (METs), which indicate oxygen consumption while sitting at rest, to objectively quantify the intensity of PA.[31] Physical activity was divided into three categories by intensity equivalent according to recommendations for exercise prescriptions: (1) light-intensity (<3.0 METs), slow walking at a speed of around 2 miles per hour (e.g., walking for leisure or to work); (2) moderate-intensity (3.0—5.9 METs), PA that make you breathe a little heavily (e.g., walking briskly at a speed of 2.5—4.0 miles per hour, mopping, biking at a moderate pace, or playing doubles tennis); (3) vigorous-intensity (≥6 METs), strenuous PA that makes you breathe quite heavily (e.g. running, climbing, or brisk biking).[32—34]

The total amount of PA considered the intensity, duration, and frequency in the form of METs-minutes per week (METs-Min/Week), which was calculated by the following formula: 2.2 * 30 * (days with light-intensity PA for ≥30 min) + 4 * 30 * (days with moderate-intensity PAs for ≥30 min) + 7 * 20 * (days with vigorous-intensity PAs for ≥20 min). We used the mean MET values for each PA code within a specific intensity PA group, as presented in the 2011 Compendium of Physical Activities,[35] as the coefficient for each item in the formula (https://sites.google.com/site/compendiumofphysicalactivities/home).

Lastly, we divided the amount of PA into five categories: (1) none or sedentary, 0 METs-Min/Week, (2) mild, 0 < METs-Min/Week <500, (3) moderate, 500 ≤ METs-Min/Week <1000, (4) severe, 1000 ≤ METs-Min/Week <1500, and (5) extreme, ≥1500 METs-Min/Week.[33,36]

Definition of clinical variables

Community-onset or healthcare facility—associated sepsis was identified using International Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes for sepsis or systemic inflammatory response syndrome, except for newborn (P36) and puerperal (O85) (Table S2).[37] To address the limitations of operationally defining the diagnosis based on ICD-10 codes, we used only sepsis-related codes accompanied by hospital admissions, excluding cases in which a sepsis-related diagnostic code was input for an outpatient. Total number of adult patients hospitalized with sepsis by ICD-10 code and year are described in the additional file (Table S3).

We identified comorbidities by applying the diagnostic criteria of 2009, when the HEALS exams were conducted (Table S4). Dyslipidemia was defined as a fasting total cholesterol ≥240 mg/dL or a patient taking hyperlipidemia agents with ICD-10 E78, and DM was defined as glucose ≥126 mg/dL or a patient taking anti-diabetic drugs with ICD-10 E11—14. Hypertension was defined as a systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg or a patient taking anti-hypertensive drugs with ICD-10 I10—I13, I15. Chronic kidney diseases (CKD) were diagnosed as an estimated glomerular filtration rate <60 mL/min/1.73 m^2, as calculated by the Modification of Diet in Renal Disease equation.

Chronic diseases included the nine illness groups (chronic lung diseases, chronic liver diseases, CKD, cardiovascular diseases, cerebrovascular accidents, solid cancers, hematologic malignancies without hematopoietic stem cell transplantation, and solid organ or hematopoietic stem cell transplant recipients), and were extracted from the KNHIS database using ICD-10 codes, except for CKD (Table S4). Body mass index (BMI) was classified as underweight (<18.5 kg/m^2), normal (18.5—22.9 kg/m^2), pre-obese (23—24.9 kg/m^2), obese class I (25—29.9 kg/m^2), and obese class II (≥30 kg/m^2).[38] Abdominal obesity was defined as a waist circumference ≥90 cm in males and ≥85 cm in females.[38] Alcohol consumption was categorized as none (0 g/day), mild—moderate (<30 g/day), and heavy (≥30 g/day).[39] The lowest income status (Q1) was defined as an annual household income lower than the 25th percentile based on the results of the 2010 South Korea Population and Housing Census.

Statistical analysis

Continuous variables were presented as mean ± standard deviation or median (interquartile range [IQR]), and data between the PA groups were compared using the one-way analysis of variance (ANOVA) or Kruskal—Wallis test. Categorical variables were expressed as numbers (percentages), and were compared using the chi-square test. Also, we used univariable (unadjusted model) and multivariable logistic regression or Cox's proportional regression analyses to obtain unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs) that revealed the independent difference in the incidence rate (IR) of sepsis or mortality according to the amount of PA after adjusting for age and sex (model 1) or age, sex, income, BMI, smoking, drinking, DM, hypertension, dyslipidemia, and chronic diseases (model 2). In each model, HRs were calculated using the sedentary group as the reference. All statistical analyses were performed with the SAS program (version 9.4), and two-tailed *P*-values 0.05 were considered statistically significant. Survival curves and forest plots were visualized using SAS and R-language (version 4.3.1), respectively.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine (Reg. No: 3-2023-0267). A waiver of informed consent and relevant permission forms were obtained from the National Health Insurance Sharing Service.

Results

Baseline characteristics

During a median follow-up period of 10.3 (IQR, 10.1—10.6) years, 83,011 sepsis occurred (Fig. 1). The mean age of all subjects at the time of the health screening was 47.2 years, and 13.1% of the cohort belonged to the 65 years or older group. The median amount of PA in all subjects was 330 (IQR, 66—652) METs-Min/Week, with 24.4% of the cohort not engaging in PA and 21.9% performing a moderate amount of PA. Compared with the group with non-PA, the extreme-PA group was older (51.5 vs. 49.9 years) and had a higher proportion of males (62.0% vs. 48.3%), BMI above 25 kg/m^2 (36.1% vs. 32.6%), ex-smokers (20.0% vs. 9.5%), DM (12.4% vs. 9.5%), hypertension (32.1% vs. 28.5%), dyslipidemia (19.6% vs. 18.6%), and chronic diseases (27.6% vs. 25.9%) (all $P < 0.001$) (Table 1).

Effect of physical activity on the occurrence of sepsis

The moderate-PA group (IR, 1.6/1000 person-years) had the lowest unadjusted HR of sepsis incidence (HR, 0.53; 95% CI, 0.52—0.55), compared with the non-PA group (IR, 2.9/1000 person-years) (overall $P < 0.001$) (Table 2 and Fig. 2A). Multivariable models 1 and 2 both show that all adjusted HRs (aHRs) of sepsis incidence in each group that engaged in PA were significantly lower than in the non-PA group (all overall $P < 0.001$). In model 2, the moderate-PA group (aHR, 0.73; 95% CI, 0.72—0.75) had the lowest risk of sepsis among the groups (Table 2).

The risk of sepsis was significantly lower in groups that engaged in PA at light- or moderate- or vigorous-intensity for ≥5 days a week, compared to the PA groups of the same intensity for <5 days (all $P < 0.001$). According to the days of PA per week, individuals who engaged in PA once a week or daily had a significantly higher IR of sepsis compared with those who engaged in PA 3—5 times a week at any intensity (all overall $P < 0.001$) (Fig. 3A, B, and C). In particular, the IR (3.6/1000 person-years) and risk (aHR in model 2, 0.92; 95% CI, 0.89—0.96) of sepsis when engaging in vigorous-intensity PA every day was highest in all cases (Fig. 3C).

Association between physical activity and sepsis according to confounding variables

All groups who engaged in any amount of PA had significantly lower aHRs for sepsis incidence in model 2 than the non-PA group when subgroups were divided by potential confounding factors, except for the extreme-PA group that was underweight and the mild-PA group containing obese class II subjects. Physical activity in the obese class III subgroup, regardless of amount, did not decrease the risk of sepsis, but rather severe-PA (aHR, 1.94; 95% CI, 1.27—2.96) significantly increased the risk of sepsis. In particular, moderate-PA in the ex-smoker group had a

Table 1 Baseline demographic characteristics of the study population by physical activity.

Variables	Total	Amount of physical activity					
		None	Mild	Moderate	Severe	Extreme	*P*-value
		0[a]	<500[a]	500–1000[a]	1000–1500[a]	≥1500[a]	
Number (%)	3,929,165 (100)	958,067 (24.4)	1,664,751 (42.4)	861,931 (21.9)	274,078 (7.0)	170,338 (4.3)	
METs-Min/Week, median (IQR)	330 (66–652)	0 (0–0)	318 (140–396)	710 (600–850)	1238 (1110–1304)	1820 (1630–2282)	<0.001
Age, y	47.2 ± 14.0	49.9 ± 14.4	45.8 ± 14.0	45.8 ± 13.1	48.5 ± 13.3	51.5 ± 13.5	<0.001
Age groups							<0.001
<40 y	1,215,090 (30.9)	237,860 (24.8)	588,754 (35.4)	285,998 (33.2)	69,654 (25.4)	32,824 (19.3)	
40–64 y	2,201,257 (56.0)	550,166 (57.4)	880,299 (52.9)	495,577 (57.5)	169,364 (61.8)	105,851 (62.1)	
≥65 y	512,818 (13.1)	170,041 (17.8)	195,698 (11.8)	80,356 (9.3)	35,060 (12.8)	31,663 (18.6)	
Sex							<0.001
Male	2,143,763 (54.6)	463,130 (48.3)	881,099 (52.9)	529,006 (61.4)	164,995 (60.2)	105,533 (62.0)	
Female	1,785,402 (45.4)	494,937 (51.7)	783,652 (47.1)	332,925 (38.6)	109,083 (39.8)	64,805 (38.0)	
BP, mmHg							
Systolic	122.5 ± 15.1	123.2 ± 15.7	121.7 ± 14.9	122.4 ± 14.6	123.3 ± 14.8	124.3 ± 15.0	<0.001
Diastolic	76.3 ± 10.1	76.6 ± 10.3	76.0 ± 10.1	76.5 ± 9.9	76.7 ± 9.9	77.0 ± 9.9	<0.001
BMI, kg/m^2	23.7 ± 3.2	23.7 ± 3.3	23.6 ± 3.3	23.9 ± 3.2	24.0 ± 3.0	24.1 ± 3.0	<0.001
BMI groups							<0.001
<18.5 kg/m^2	145,144 (3.7)	39,108 (4.1)	72,945 (4.4)	24,289 (2.8)	5784 (2.1)	3018 (1.8)	
18.5–23 kg/m^2	1,533,452 (39.0)	377,160 (39.4)	674,216 (40.5)	324,227 (37.6)	98,864 (36.1)	58,985 (34.6)	
23–25 kg/m^2	968,102 (24.6)	228,979 (23.9)	396,340 (23.8)	221,610 (25.7)	74,202 (27.1)	46,971 (27.6)	
25–30 kg/m^2	1,142,997 (29.1)	276,980 (28.9)	463,609 (27.9)	260,829 (30.3)	85,915 (31.4)	55,664 (32.7)	
≥30 kg/m^2	139,470 (3.6)	35,840 (3.7)	57,641 (3.5)	30,976 (3.6)	9313 (3.4)	5700 (3.4)	
Smoking							<0.001
Non-smoker	2,342,841 (59.6)	637,926 (66.6)	993,658 (59.7)	463,603 (53.8)	151,192 (55.2)	96,462 (56.6)	
Ex-smoker	563,291 (14.3)	91,081 (9.5)	225,514 (13.6)	157,466 (18.3)	55,175 (20.1)	34,055 (20.0)	
Current smoker	1,023,033 (26.0)	229,060 (23.9)	445,579 (26.8)	240,862 (27.9)	67,711 (24.7)	39,821 (23.4)	
Drinking[b]							<0.001
No	2,029,912 (51.7)	606,835 (63.3)	836,558 (50.3)	372,265 (43.2)	128,199 (46.8)	86,055 (50.5)	
Mild-moderate	1,586,915 (40.4)	279,236 (29.2)	703,141 (42.2)	415,333 (48.2)	121,369 (44.3)	67,836 (39.8)	
Heavy	312,338 (8.0)	71,996 (7.5)	125,052 (7.5)	74,333 (8.6)	24,510 (8.9)	16,447 (9.7)	
Income, lowest Q1	765,052 (19.5)	211,438 (22.1)	319,418 (19.2)	151,168 (17.5)	50,898 (18.6)	32,130 (18.9)	<0.001
DM	340,010 (8.7)	90,577 (9.5)	130,574 (7.8)	70,279 (8.2)	27,441 (10.0)	21,139 (12.4)	<0.001
Hypertension	998,210 (25.4)	272,838 (28.5)	386,965 (23.2)	207,916 (24.1)	75,894 (27.7)	54,597 (32.1)	<0.001
Dyslipidemia	680,338 (17.3)	177,738 (18.6)	274,825 (16.5)	143,980 (16.7)	50,334 (18.4)	33,461 (19.6)	<0.001

Chronic diseases[c]	919,867 (23.4)	248,310 (25.9)	274,592 (21.4)	244,631 (22.6)	97,083 (24.1)	55,251 (27.6)	<0.001
Lung	324,015 (8.2)	90,453 (9.4)	100,273 (7.8)	83,497 (7.7)	32,162 (8.0)	17,630 (8.8)	<0.001
Liver	137,984 (3.5)	36,099 (3.8)	40,693 (3.2)	36,923 (3.4)	15,418 (3.8)	8851 (4.4)	<0.001
CKD	271,824 (6.9)	70,267 (7.3)	109,426 (6.6)	58,641 (6.8)	20,004 (7.3)	13,486 (7.9)	<0.001
CVD	173,787 (4.4)	49,931 (5.2)	48,579 (3.8)	45,174 (4.2)	18,476 (4.6)	11,627 (5.8)	<0.001
CVA	80,939 (2.1)	25,620 (2.7)	21,822 (1.7)	20,186 (1.9)	7905 (2.0)	5406 (2.7)	<0.001
Solid cancers	35,457 (0.9)	8452 (0.9)	9648 (0.8)	9890 (0.9)	4437 (1.1)	3030 (1.5)	<0.001
Hematologic malignancies[d]	1928 (<0.1)	482 (<0.1)	556 (<0.1)	524 (<0.1)	236 (<0.1)	130 (<0.1)	0.318
SOT	1119 (<0.1)	230 (<0.1)	331 (<0.1)	335 (<0.1)	147 (<0.1)	76 (<0.1)	0.157
HSCT	154 (<0.1)	29 (<0.1)	50 (<0.1)	42 (<0.1)	23 (<0.1)	10 (<0.1)	0.210
Laboratory findings[e]							
Glucose, mg/dL	97.3 ± 23.8	97.9 ± 25.2	96.6 ± 23.2	97.1 ± 23.1	98.2 ± 23.7	99.6 ± 25.3	<0.001
Total-C, mg/dL	195.1 ± 36.8	196.0 ± 37.7	194.5 ± 36.6	194.9 ± 36.3	195.3 ± 36.4	195.2 ± 36.7	<0.001
HDL-C, mg/dL	56.1 ± 27.9	57.0 ± 36.9	55.8 ± 24.4	55.6 ± 23.4	56.2 ± 24.6	56.3 ± 25.6	<0.001
LDL-C, mg/dL	113.6 ± 38.6	114.6 ± 41.5	113.1 ± 37.6	113.3 ± 37.6	113.9 ± 37.8	114.0 ± 38.2	<0.001

[a] Indicate METs-Min/Week.
[b] Drinking was classified according to the average daily alcohol consumption: (1) no, 0 g/day; (2) mild to moderate, <30 g/day; and (3) heavy, ≥30 g/day.
[c] Number of subject with at least one of the disease groups, excluding the duplicated cases with multiple illnesses simultaneously.
[d] Without HSCT.
[e] Measured after fasting for more than 12 h.

Data are expressed as mean ± standard deviation or median (interquartile range) or number (percentage).

Abbreviations, BMI, body mass index; BP, blood pressure; C, cholesterol; CKD, chronic kidney diseases; CVA, cerebrovascular accidents; CVD, cardiovascular diseases; DM, diabetes; HDL, high density lipoprotein; HSCT, hematopoietic stem cell transplantation; IQR, interquartile; LDL, low density lipoprotein; MET, metabolic equivalent; SOT, solid organ transplantation; Q, quartile; y, years.

Table 2 The effects of physical activity on the incidence of sepsis.

Physical activity	Subjects	Follow-up duration[b]	Sepsis		HR (95% CI)		
			No.	IR[c]	Unadjusted model	Multivariable model 1	Multivariable model 2
None (0[a])	958,067	9,553,614	27,789	2.909	1 (Ref.)	1 (Ref.)	1 (Ref.)
Mild (<500[a])	1,664,751	16,812,756	31,844	1.894	0.651 (0.640–0.661)	0.870 (0.856–0.884)	0.880 (0.865–0.896)
Moderate (500–1000[a])	861,931	8,753,450	13,646	1.559	0.534 (0.523–0.545)	0.758 (0.743–0.774)	0.733 (0.717–0.748)
Severe (1000–1500[a])	274,078	2,773,887	5422	1.955	0.670 (0.651–0.690)	0.769 (0.747–0.791)	0.787 (0.767–0.808)
Extreme (≥1500[a])	170,338	1,710,923	4310	2.519	0.864 (0.837–0.892)	0.772 (0.746–0.796)	0.798 (0.774–0.823)
Overall *P*-value[d]					<0.001	<0.001	<0.001

[a] METs-Min/Week.
[b] Person-years.
[c] Per 1000 person-years.
[d] From the ANOVA test.
Multivariable model 1 was adjusted for age and sex. Multivariable model 2 was adjusted for age, sex, income, body mass index, smoking, drinking, diabetes, hypertension, dyslipidemia, and chronic diseases.
Abbreviations: CI, Confidence interval; HR, hazard ratio; IR, incidence rate; MET, metabolic equivalent; No., number; Ref., reference.

significantly lowest sepsis risk than non-PA group (aHR, 0.68; 95% CI, 0.64–0.71), and the lowest IR (1.46/1000 person-years) was observed in current smoker and moderate-PA group (Table S5).

The male subjects who performed any amount of PA had significantly lower risk of sepsis compared to the male group with non-PA, especially showing the lowest IR (1.61/1000 person-years) and risk (aHR, 0.75; 95% CI, 0.73–0.77) in the moderate-PA group. Physical activity was also associated with a lower risk of sepsis in the female subjects, with the lowest IR (1.49/1000 person-years) in the moderate-PA group (Fig. S1A). Among people younger than 40 years, the incidence of sepsis with any amount of PA was similar to that in the non-PA group. Any amount of PA by adults older than 65 years significantly reduced the risk of sepsis compared with subjects younger than 40 years who engaged in the same level of PA (Fig. S1B).

Effect of physical activity on all-cause mortality after sepsis

The unadjusted long-term all-cause of mortality after sepsis was lowest in the moderate-PA group (268/1000 patient-years). The overall probability of mortality during the observation period in the PA groups was significantly lower than in the non-PA group in model 2 ($P = 0.003$) (Fig. 2B and Table S6). All-cause mortality within 30 days after diagnosis of sepsis did not differ significantly between the non-PA group and any PA group ($P = 0.355$ in model 2) (Fig. 2C and Table S6).

Discussion

The protective effect of PA against the occurrence of sepsis was more pronounced with non-excessive PA, especially among elderly subjects and ex-smokers. On the other hand, PA was found to have no effect in severely obese subjects or subjects younger than 40 years. Overall, the effect of PA on lowering the risk of sepsis was greatest when a moderate amount of PA was performed 3–5 days a week, with daily PA of vigorous-intensity having the least influence. Our definition of moderate PA is equivalent to the 2020 WHO guidelines for PA to improve health in adults, which recommend 150–300 min of moderate-intensity or 75–150 min of vigorous-intensity PA per week.[40]

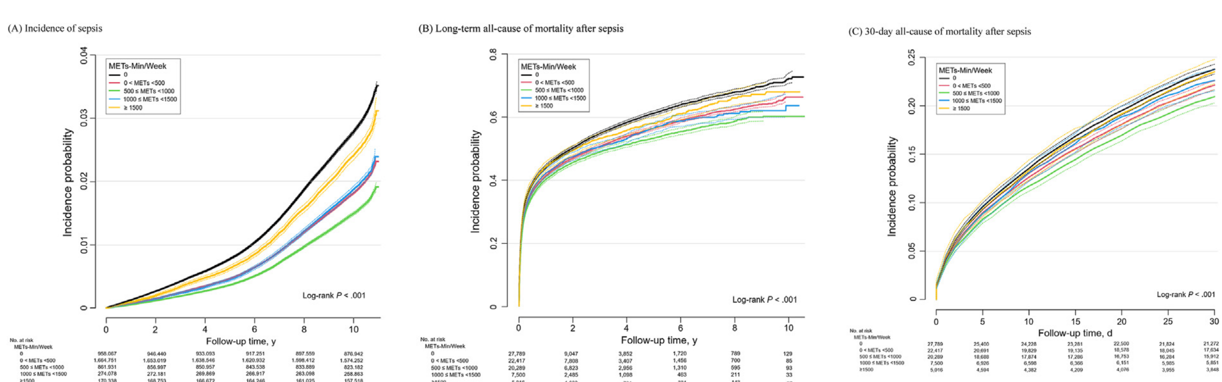

Figure 2. Unadjusted probabilities of sepsis incidence and mortality after sepsis according to the amount of physical activity. The dotted line represents the 95% confidence interval. Abbreviations. MET, metabolic equivalent.

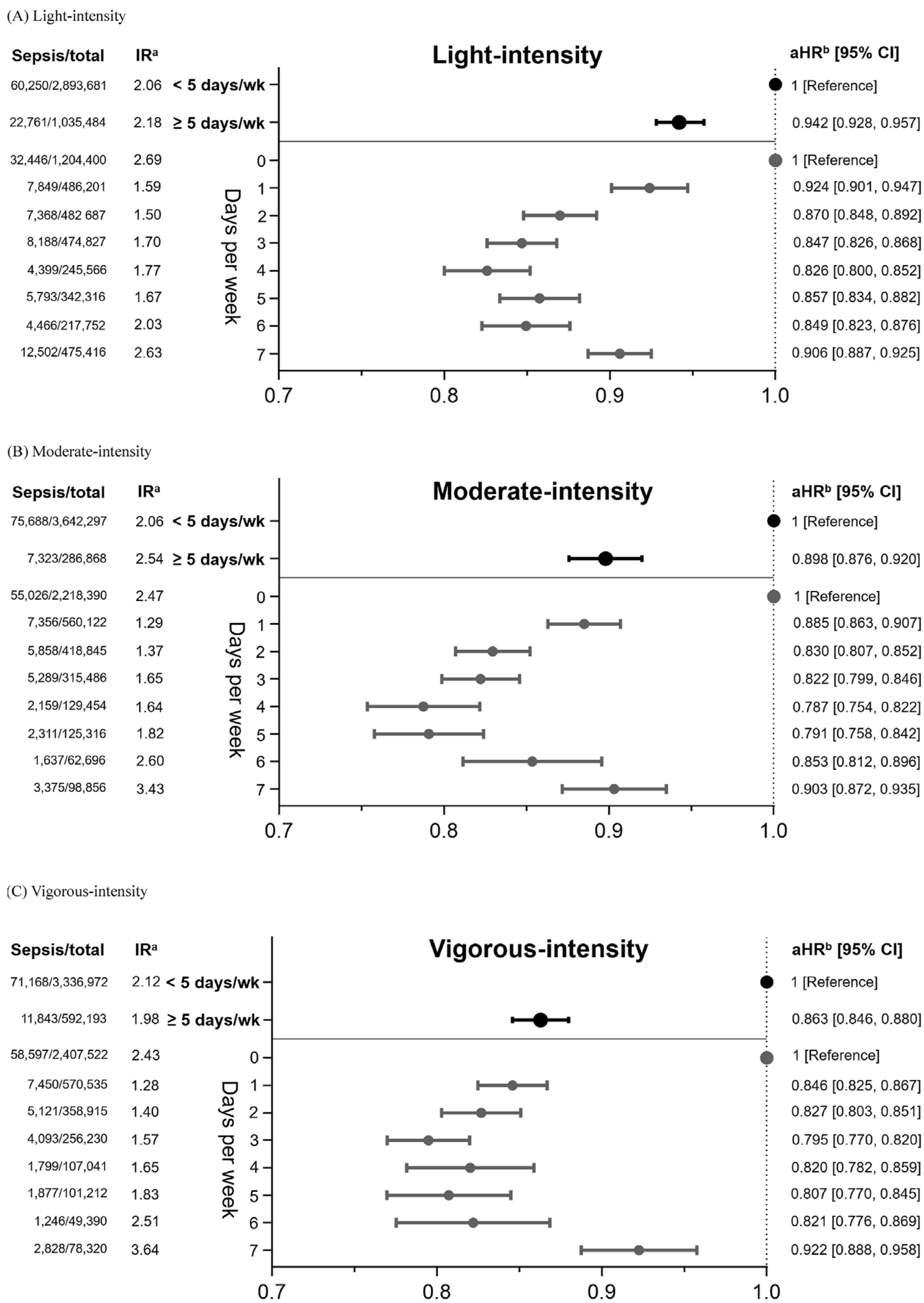

Figure 3. Differences in sepsis incidence according to the intensity of physical activity. [a]Per 1000 person-years, [b]Adjusted for age, sex, income, body mass index, smoking, drinking, diabetes, hypertension, dyslipidemia, and chronic diseases. Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; IR, incidence rate.

Our enormous number of follow-up subjects and sepsis patients, 4 million and 83,011, respectively, could considerably reduce the possibility of random error that can result from imprecision or loss in event selection, as well as the recall or memory decay bias associated with self-reports. The diagnostic codes we used should be exact to make claims and ensure reimbursement from the KNHIS, which should decrease errors or omissions of a sepsis diagnosis as a critical illness. Wang et al. reported that, in a cohort of 30,000 adults aged 45 years and older, sedentary subjects had an approximately 30% higher risk of sepsis than the group with a high frequency of PA per week, but they did not consider PA intensity, type, or duration.[41] The modulation of immune systems against infection could vary depending on the type, intensity, and volume of PA.[42] Our study has the strength of being the largest and longest observational cohort analyzed to estimate the association of PA with community- or hospital-acquired sepsis using METs-Min/Week as an objective indicator of PA amounts.

Previous studies in various animal models showed that moderate PA can improve the risk of infection, severity of or mortality from sepsis, and an adequate immune response in septic conditions compared with a sedentary control or heavy PA, which was expressed as an inverted J curve or open-window immune-impairment hypothesis.[22,23,42–47] Vigorous- or near-maximal PA that greatly increases the consumption of oxygen and energy might suppress the innate and adaptive immune responses.[48–50] No research has examined how aerobic PA alters the immune systems after sepsis in humans. PA in sepsis animal experiments was associated with a decrease of inflammatory detriment in the lung and apoptosis in end-organ tissues, as well as protection against oxidative damage and acute kidney injury.[22,43,45,51] IL-6, a frontline cytokine excreted from muscles during PA, promotes lipolysis and free fatty acid oxidation, as well as the generation of reactive oxygen species, which can lead to a balance between the antioxidant system and the anti-inflammatory response.[42,52,53] Various anti-inflammatory responses guided by non-excessive PA contributes to prevent the development of sepsis by modulating disproportionate inflammatory responses.[42,53]

An important finding of our study is that the protective effect of PA on sepsis is more prominent in elderly adults, who are at the highest risk of and have the worst outcomes from sepsis.[54] The high incidence (11.2/1000 person-years) of sepsis in subjects aged 65 years or older with sedentary behavior was significantly reduced, by 7.9–9.5/1000 person-years, in subjects who engaged in PA of any amount. Even without resistance or endurance training, suitable aerobic PA in daily life could reduce the risk of sepsis in elderly people by 25%. An animal study supports these results.[46] Running aged mice diminished the overwhelming sepsis-induced pro-inflammatory and pro-coagulant responses by improving endothelial function or capillary plugging and upregulating endothelial nitric oxide synthase.[46] Further experiments are warranted to determine whether PA can restore the age-related immunosenescence of humoral or cell-mediated immunity.

The long-term reduction in the all-cause death after sepsis associated with physical enhancement could be considered as one positive effect of PA in terms of prolonging life expectancy, particularly in the elderly. Because the functional fragility after sepsis can be long-lasting and irreversible despite providing intensive physical therapy during acute sepsis, our finding that sepsis might be preventable through lifestyle modification, the same as other chronic diseases, wound represents an advance of a different perspective in sepsis managements.

Study limitations

This study has several limitations. First, sepsis events were identified based on ICD-10 codes, which might be biased by their operational definitions. Additionally, the definition or scope of sepsis was changed to Sepsis-3 in 2016.[1] Many of the subjects would have been diagnosed according to the 2001 International Sepsis Definitions Consensus that includes systemic inflammatory response syndrome and severe sepsis.[55] Although the details of the sepsis codes in ICD-10 did not change during the study period, that would not necessarily guarantee that the altered definition of sepsis was applied accurately. Second, physician judgment about the likelihood of infection could increase the chance that sepsis would be under- or over-diagnosed. Third, the performance of PA was assessed by a self-report questionnaire that might under- or over-report the actual activity. Fourth, serial follow-up on the contents of the questionnaire in all subjects was not conducted. Therefore, our study presumes that the subjects generally had a high tendency to be consistent in the PA habits they reported in a single survey.[27,28] In fact, the fallow-up data for same recall questionnaire in cohort subjects (N = 9,735,404) who underwent biennial checkups twice showed no differences in total amount of PA (Table S7). Lastly, because we did not measure the functional performance, the subjects with poorer health statuses or chronic illnesses could not do intense PA. Although most of our cohort consisted of people who would be physically active and of an age where voluntary health checkup was capable, conditions that made PA difficult and thus induced a higher risk for sepsis would develop during long-term follow-up.

Conclusions

In a study with 10 years of follow-up for 4 million adults, non-heavy PA was associated with a lower risk of sepsis, and that relationship was especially noticeable in elderly subjects. With support from the results of future well-organized prospective clinical trials, regular and non-excessive aerobic PA, which are undemanding to practice in daily life, could be a useful individualized precautionary measure against sepsis.

CRediT authorship contribution statement

Kyoung Hwa Lee: Writing – review & editing, Writing – original draft, Visualization, Data curation, Conceptualization. **Eun Hwa Lee:** Writing – review & editing, Writing – original draft, Project administration. **Kyu-na Lee:** Visualization, Validation, Methodology, Data curation. **Yebin Park:** Writing – original draft, Visualization, Validation, Data curation. **Young Goo Song:** Supervision, Project administration. **Kyung Do Han:** Visualization, Validation, Supervision, Methodology, Data curation, Conceptualization. **Sang Hoon Han:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Formal analysis, Conceptualization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2024.04.009.